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Mechanisms of Antiaddictive Actions of Ibogaine^a

STANLEY D. GLICK^b AND ISABELLE M. MAISONNEUVE

Department of Pharmacology and Neuroscience, A-136, Albany Medical College, Albany, New York 12208, USA

ABSTRACT: Ibogaine, an alkaloid extracted from *Tabernanthe iboga*, is being studied as a potential long-acting treatment for opioid and stimulant abuse as well as for alcoholism and smoking. Studies in this laboratory have used animal models to characterize ibogaine's interactions with drugs of abuse, and to investigate the mechanisms responsible. Ibogaine, as well as its metabolite, noribogaine, can decrease both morphine and cocaine self-administration for several days in some rats; shorter-lasting effects appear to occur on ethanol and nicotine intake. Acutely, both ibogaine and noribogaine decrease extracellular levels of dopamine in the nucleus accumbens of the rat brain. Ibogaine pretreatment (19 hours beforehand) blocks morphine-induced dopamine release and morphine-induced locomotor hyperactivity while, in contrast, it enhances similar effects of stimulants (cocaine and amphetamine). Ibogaine pretreatment also blocks nicotine-induced dopamine release. Both ibogaine and noribogaine bind to kappa opioid and *N*-methyl-D-aspartate (NMDA) receptors and to serotonin uptake sites; ibogaine also binds to sigma-2 and nicotinic receptors. The relative contributions of these actions are being assessed. Our ongoing studies in rats suggest that kappa agonist and NMDA antagonist actions contribute to ibogaine's effects on opioid and stimulant self-administration, while the serotonergic actions may be more important for ibogaine-induced decreases in alcohol intake. A nicotinic antagonist action may mediate ibogaine-induced reduction of nicotine preferences in rats. A sigma-2 action of ibogaine appears to mediate its neurotoxicity. Some effects of ibogaine (*e.g.*, on morphine and cocaine self-administration, morphine-induced hyperactivity, cocaine-induced increases in nucleus accumbens dopamine) are mimicked by a kappa agonist (U50,488) and/or a NMDA antagonist (MK-801). Moreover, a combination of a kappa antagonist and a NMDA agonist will partially reverse several of ibogaine's effects. Ibogaine's long-term effects may be mediated by slow release from fat tissue (where ibogaine is sequestered) and conversion to noribogaine. Different receptors, or combinations of receptors, may mediate interactions of ibogaine with different drugs of abuse.

INTRODUCTION

Ibogaine, an alkaloid extracted from *Tabernanthe iboga*, is being studied as a potential long-acting treatment for opioid and stimulant abuse as well as for alcoholism and smoking. Studies in this laboratory have used animal models to characterize ibogaine's interactions with drugs of abuse, and to investigate the mechanisms responsible.

Ibogaine and its active metabolite noribogaine^{6,11} appear to have multiple mechanisms of action in the nervous system. TABLE 1 shows the reported affinities of ibogaine and noribogaine for several binding sites. The evidence to date suggests that actions at

^a This research was supported by NIDA Grant DA 03817.

^b Corresponding author. Tel: (518) 262-5303; fax: (518) 262-5799; email: sglick@ccgateway.amc.edu

TABLE 1. Ibogaine and Noribogaine Binding Affinities (Ki)

	Ibogaine		Noribogaine	
Kappa opioid	2–4 μ M	(3,7,9)	1 μ M	(7)
Mu opioid	10–100 μ M	(3,7,10)	3 μ M	(7)
Delta opioid	>100 μ M	(3,7)	25 μ M	(7)
NMDA	1–3 μ M	(4,8,10)	6 μ M	(4)
Sigma-1	9 μ M	(2,5)	15 μ M	(2)
Sigma-2	0.09–0.2 μ M	(2,5)	5 μ M	(2)
Dopamine transporter	2 μ M	(6)	2 μ M	(6)
Serotonin transporter	0.5 μ M	(6)	0.04 μ M	(6)
Nicotinic (IC₅₀)	0.02 μ M	(1)	1.5 μ M	(1)

References:

1. Badio *et al.*
2. Bowen *et al.*
3. Deecher *et al.*
4. Layer *et al.*
5. Mach *et al.*
6. Mash *et al.*
7. Pearl *et al.*
8. Popik *et al.*
9. Repke *et al.*
10. Sweetnam *et al.*

several of these sites may together mediate ibogaine's putative antiaddictive effects. Indeed it is difficult to imagine that a treatment could be effective in so many diverse addictions without itself having a plethora of actions. Hence the basic premise of this paper is that ibogaine has a complex pharmacology; and it may be precisely because of this that ibogaine has a peculiarly novel efficacy.

MATERIALS AND METHODS

Animals

All subjects were naive female Sprague-Dawley (Taconic) or Long-Evans (Charles River) rats, approximately 3 months old and weighing 230–250 g at the beginning of an experiment. Rats were maintained on a normal light/dark cycle (lights on/off at 0700 hr/1900hr).

Drug Self-Administration

The intravenous self-administration procedure has been described previously.^{12–14} Briefly, responses on either of two levers (mounted 15 cm apart on the front wall of each operant test cage) were recorded on an IBM compatible 486 computer with a Med Associates, Inc. interface. The intravenous self-administration system consisted of polyethylene-silicone cannulas constructed according to the design of Weeks,¹⁵ Instech harnesses and commutators, and Harvard Apparatus infusion pumps (#55-2222). Shaping of the bar-press response was initially accomplished by training rats to bar-press for water. Cannulas were then implanted in the external jugular vein according to

procedures described by Weeks.¹⁵ Self-administration testing began with a 16-hr nocturnal session followed by daily 1-hr sessions, 5 days (Monday–Friday) a week. A lever-press response produced a 10- or 50- μ l infusion of drug solution, 0.01 mg morphine sulfate or 0.1 mg cocaine hydrochloride, respectively, in 0.2–1.0 second. Since all rats generally weighed 250 ± 20 g, each response delivered approximately 0.04 mg/kg of morphine or 0.4 mg/kg cocaine.

Nicotine was self-administered via the oral route using an operant procedure previously described.¹⁶ Two fluid delivery systems, each consisting of a fluid container connected to a solenoid, delivered 0.1 ml nicotine solution or water to stainless steel drinking cups located above each of two levers. An aqueous solution of nicotine bitartrate was made at a concentration of 4 μ g/ml (1.4 μ g/ml of the base); the solution was adjusted to a pH of 7.0. Rats were initially placed into the operant chambers overnight and trained to respond for water, using both levers, on a continuous reinforcement schedule. Following nocturnal training, rats were switched to 1-hr sessions during the day, five days a week (Monday–Friday), and maintained on a 23-hr water deprivation schedule. Rats were provided *ad libitum* access to water after test sessions on Fridays, with the water deprivation schedule reinstated on Sundays in preparation for Mondays' test sessions. After five consecutive daily sessions in which rats made at least 50 responses/hr, nicotine was introduced. Rats received nicotine by pressing one lever and water by pressing the other. Side of presentation of nicotine was alternated each day.

Locomotor Activity

Locomotor activity was assessed using cylindrical photocell activity cages (60 cm, three crossing beams) interfaced to an IBM compatible 486 computer.¹⁷ Interruptions of light beams were recorded with the software Med-PC (MED Associates, St. Albans, VT).

In Vivo Microdialysis

The microdialysis procedures used to assess effects of drug treatments on extracellular levels of dopamine and its metabolites have been used extensively in this laboratory.^{11,13,14,18,19} Briefly, under pentobarbital anesthesia, rats were implanted stereotactically with guide cannulas so that, when inserted, the tips of the dialysis probes would be located in the intended brain areas (e.g., nucleus accumbens, striatum, medial prefrontal cortex). Each cannula was fixed firmly in the skull with dental cement.

At least four days after surgery, a rat was placed in a dialysis chamber, a cylindrical (30 cm diameter) Plexiglas cage providing free access to food and water. The probe (2 or 3 mm; CMA) was then lowered into the guide cannula. The dialysis probe was continuously perfused with a solution containing 146 mM NaCl, 2.7 mM KCl, 1.2 mM CaCl_2 , and 1.0 mM MgCl_2 at a flow rate of 1 μ l/min. On the next morning (15–20 hr later), the dialysis experiment was carried out on a freely moving animal. Twenty-minute fractions were collected in vials containing 2 μ l of 1.1 N perchloric acid solution (containing 5 mg/l EDTA and 5 mg/l sodium metabisulfite). Upon completion of an experiment, rats were killed and histological analysis of each brain was performed to verify the locations of the probes.

Perfusate samples were analyzed by high-performance liquid chromatography with electrochemical detection (HPLC-ECD). The HPLC consisted of a Waters pump (model 510), a WISP autosampler (model 712), a Phase Separation Spherisorb C-18 column (S3 ODS2; 10 cm $\times$ 4.6 mm) and a Waters detector (model 464). The mobile

phase consisted of 6.9 g/l sodium monobasic phosphate, 450 mg/l heptane sulfonic acid, 80 mg/l disodium EDTA, and 110 ml/l methanol; the solution was adjusted with HCl to pH 3.7 and was pumped at a rate of 1.2 ml/min. Chromatograms were processed using Hewlett-Packard HPLC 2D Chem Station software.

RESULTS

Ibogaine (40 mg/kg, intraperitoneally (i.p.), administered 15 min prior to testing on Day 1) decreases both morphine and cocaine self-administration in rats^{12,13} (FIG. 1). While interpretation of ibogaine's effects on Day 1 may be confounded by nonspecific motor effects (e.g., tremor), the significant effects on Day 2 occur at a time when motor behavior appears to be normal. Consistent with this, ibogaine decreases responding for water on Day 1 but not thereafter.¹² Furthermore, in some rats (about 35% of rats tested), ibogaine decreases morphine or cocaine intake for several days (up to three weeks) after a single ibogaine administration.

The effects of ibogaine on morphine self-administration appear to be at least partially mediated by a combination of kappa opioid agonist and *N*-methyl-D-aspartate (NMDA) antagonist actions. Thus a combination of a kappa opioid antagonist (nor-binaltorphimine; norBNI) and an NMDA agonist (NMDA) significantly antagonized ibogaine (FIG. 2a), while neither norBNI nor NMDA alone had this effect.²⁰

Other effects of ibogaine can also be blocked by a combination of norBNI and NMDA.²⁰ These include ibogaine (40 mg/kg, i.p., administered 19 hr beforehand) inhibition of morphine-induced (5 mg/kg, i.p.) locomotor stimulation (FIG. 2b) and ibogaine inhibition of dopamine release in the striatum (FIG. 2c).

The results from studies of the effects of kappa agonist (U50, 488 and spiradoline) and NMDA antagonist (MK-801) agents complement the results above. Both kinds of agents inhibit morphine-induced locomotor stimulation in a manner resembling that of ibogaine.^{21,22} Kappa agonists also decrease both morphine and cocaine self-administration in rats.²³ However, MK-801, while it decreases morphine self-administration (and at a time, Day 2, when it does not affect responding for water), does not consistently affect cocaine self-administration (FIG. 3).

Several studies have reported that ibogaine attenuates some signs of morphine withdrawal.^{8,24,25} Layer *et al.*⁴ have correlated this effect of ibogaine with its NMDA antagonist action.

A relatively high affinity of ibogaine for nicotinic receptors¹ is consistent with the results of studies demonstrating functional interactions of ibogaine with nicotine. Ibogaine pretreatment has been shown to block nicotine-induced dopamine release in the nucleus accumbens.^{19,26} Ibogaine also reduces a preference for orally self-administered nicotine at a time (Day 2) when total rates of responding for water or nicotine are unaffected (FIG. 4).

Noribogaine has about a tenfold higher affinity for the serotonin transporter than ibogaine and, consistent with this, noribogaine is much more potent than ibogaine in raising extracellular levels of serotonin in the nucleus accumbens.⁶ However, the efficacy of ibogaine to increase serotonin levels appears to be substantially greater than that of noribogaine.²⁷ Preliminary data suggest that while noribogaine may be more effective than ibogaine in inhibiting reuptake of serotonin, ibogaine may directly release serotonin. Compared to its effects on the dopamine systems, these serotonergic effects of ibogaine and noribogaine appear to be relatively short lasting, dissipating within three hours. Similarly, while effects of ibogaine on tissue levels of dopamine metabolites are still apparent on the day after administration,^{28,29} there are no effects on tissue levels of serotonin's metabolite.²⁹ Rezvani *et al.*³⁰ have reported that ibogaine decreases alcohol

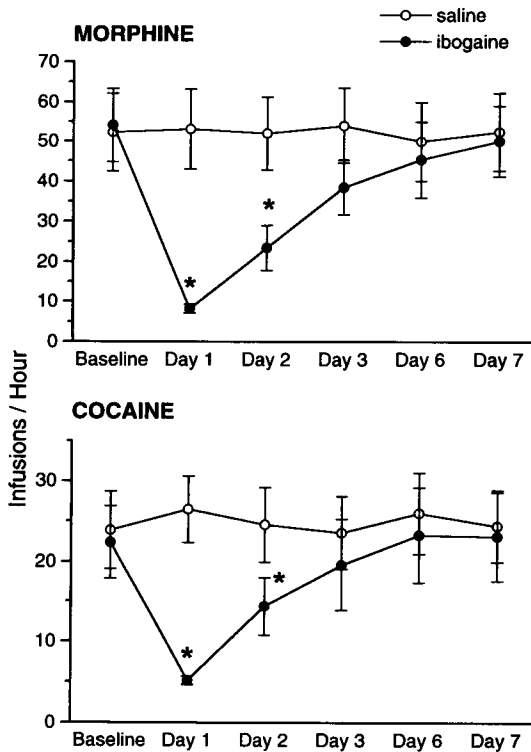


FIGURE 1. Effects of ibogaine (40 mg/kg, i.p., administered 15 minutes before testing on Day 1) on morphine and cocaine self-administration in rats. Asterisks indicate significant differences ($p < 0.05-0.01$) from saline.

intake in alcohol-preferring strains of rats and have suggested that this effect may be serotonergically mediated. The effect of ibogaine on alcohol intake seems to be apparent only on the day of ibogaine administration, consistent with ibogaine's effects on serotonin neurons. Serotonin also seems to play at least some role in mediating the discriminative stimulus effect of ibogaine in rats,^{31,32} and perhaps its acute hallucinogenic effect in humans.

O'Hearn and Molliver^{33,34} originally reported that a very high dose (100 mg/kg) of ibogaine damaged Purkinje cells in the cerebellar vermis of rats. However, subsequent studies by others have shown that the neurotoxicity is dose dependent and species specific. In rats, Molinari *et al.*³⁵ observed the expected cerebellar damage after 100 mg/kg but could detect no damage after 40 mg/kg. Scallet *et al.*³⁶ also replicated the high-dose damage in rats but detected no damage following 100 mg/kg of ibogaine administered to mice. Repeated administration of lower doses (10 mg/kg) of ibogaine has also been shown to produce no cerebellar toxicity.³⁷ Toxicity after exposure to high concentrations of ibogaine is also apparent in cerebellar cultures;³⁸ structure-activity studies using this system have suggested that the neurotoxic effect of ibogaine is mediated by sigma-2 receptors. The neurotoxic effect appears to be entirely dissociable from the putative an-

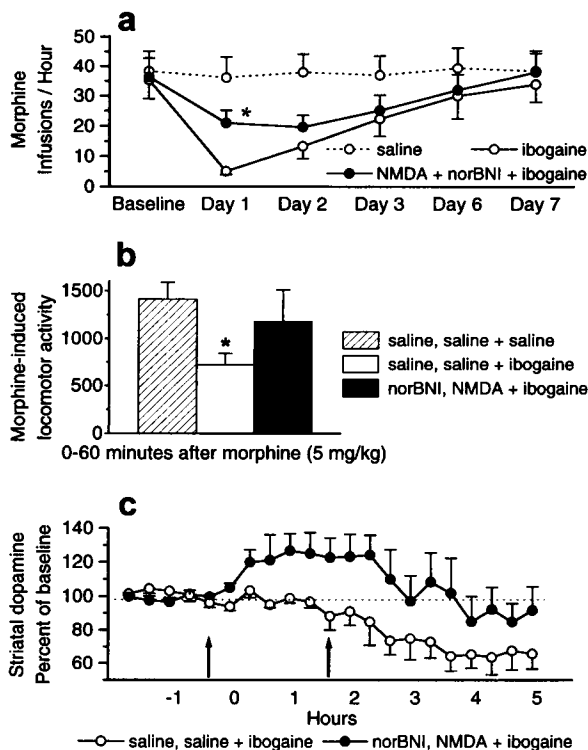


FIGURE 2. Antagonism of ibogaine (40 mg/kg, i.p.) by a combination of NMDA (20 mg/kg, i.p.) and norBNI (10 mg/kg, subcutaneously (s.c.)): **(a)** morphine self-administration (*asterisk* indicates significant difference from ibogaine alone, $p < 0.02$); **(b)** morphine-induced (5 mg/kg, i.p.) locomotor stimulation (*asterisk* indicates significant difference from saline, saline + saline); **(c)** ibogaine-induced decrease in extracellular levels of striatal dopamine (significant difference between groups, $p < 0.05$).

tiaddictive action. 18-Methoxycoronaridine (18-MC), an ibogaine derivative, mimics ibogaine's effects on morphine and cocaine self-administration in rats¹⁴ but, even at a very high dose (100 mg/kg), does not damage the cerebellum; 18-MC is also nontoxic in cerebellar cultures and has a very low affinity for sigma-2 receptors.^{38,39}

DISCUSSION

The development of pharmacotherapies for drug addiction has traditionally focused on single modes of action. While replacement therapies, *e.g.*, methadone for heroin and nicotine for smoking, are representative of a pharmacokinetic approach to the problem, recent efforts have been more directed to the design of what might be termed 'interference' therapies, that is, agents that would be expected to modulate or interfere with the mechanism of action of the abused drug. For example, dopamine

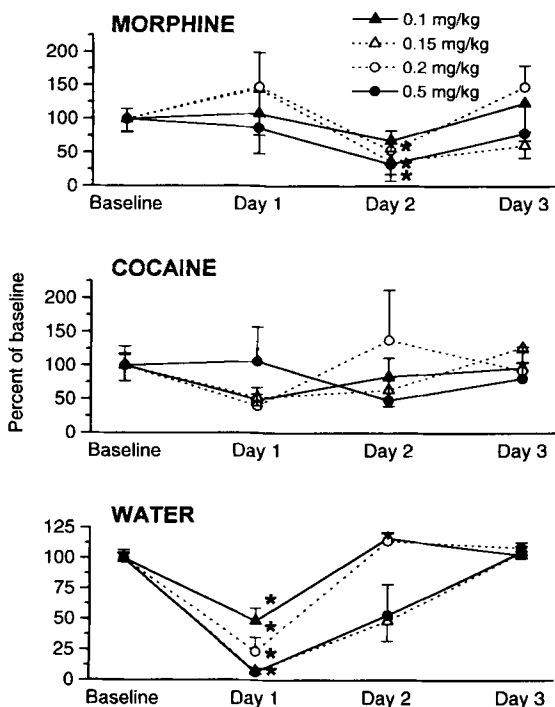


FIGURE 3. Effects of MK-801 (0.1–0.5 mg/kg, s.c.) on morphine and cocaine self-administration and on bar-pressing for water (asterisks indicate significant differences from baseline, $p < 0.05$).

transporter inhibitors, dopamine receptor agonists and antagonists, and γ -aminobutyric acid type B ($GABA_B$) receptor agonists all represent ways of blocking or dampening the consequences of a phasic increase in synaptic levels of dopamine induced by cocaine. In general, treatment drugs have been sought that are site specific, most often acting selectively at a particular receptor or receptor subtype. Viewed in this context, and depending on one's bias, the proposed use of ibogaine or related congeners to treat drug addiction, and several kinds of drug addiction at that, is heretical or revolutionary. If anecdotal reports of efficacy are ever substantiated in blinded clinical trials, the lesson to be learned from ibogaine will be clear: addiction is a complex brain disorder probably requiring a complex treatment, *i.e.*, a drug having multiple actions, or perhaps a combination of several single-action drugs. A corollary lesson that has already become evident is that science rather than politics should determine whether or not ibogaine will have any clinical utility. Indeed, the initial report of ibogaine's neurotoxicity received considerable publicity, much more than was warranted, and this was largely responsible for declining interest in ibogaine as a potentially useful antiaddictive agent. It is now clear, in view of the subsequent data (summarized above), that there was an overreaction to the neurotoxicity and that a pervasive judgment against developing ibogaine and ibogaine-like drugs was premature.

The data reviewed above indicate that there are several ways in which ibogaine

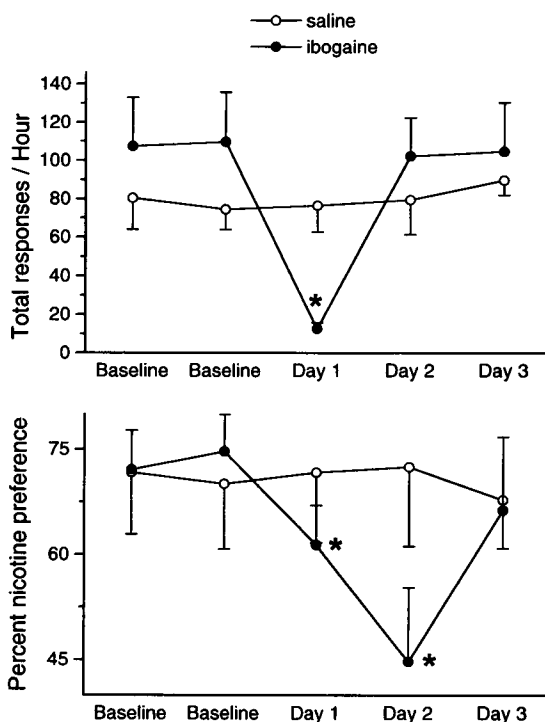


FIGURE 4. Effects of ibogaine (40 mg/kg, i.p., administered 15 minutes before testing on Day 1) on oral nicotine self-administration: total responses (*top*) and nicotine preference (*bottom*). Asterisks indicate significant differences from saline ($p < 0.05$ – 0.01).

and/or noribogaine can modulate the dopamine system in the nucleus accumbens; and it is this system that is generally considered to be the most important mediator of the addictive property of most drugs. FIGURE 5 represents a scheme in which kappa opioid agonist, NMDA antagonist and nicotinic antagonist effects of ibogaine and/or noribogaine could together dampen the responsiveness of the mesolimbic system to the dopamine-enhancing actions of addictive drugs. TABLE 2 summarizes more specifically how we presently conceive of the actions of ibogaine in relationship to its various interactions with other drugs and to its pharmacology in general.

Both kappa opioid agonist and NMDA antagonist actions appear to contribute, almost equally, to the effects of ibogaine on morphine self-administration. While a role of the kappa action in suppressing opioid withdrawal signs has not been investigated, very convincing data support a role for the NMDA action in suppressing opioid withdrawal. On the other hand, based on the effects of other kappa opioid agonist and NMDA antagonist agents, it seems that the kappa but not the NMDA action of ibogaine is important for ibogaine's effects on cocaine self-administration.

The recently reported affinity of ibogaine for nicotinic receptors is intriguing, and this is certainly consistent with the findings that ibogaine blocks nicotine-induced dopamine release as well as nicotine preferences in our oral self-administration model.

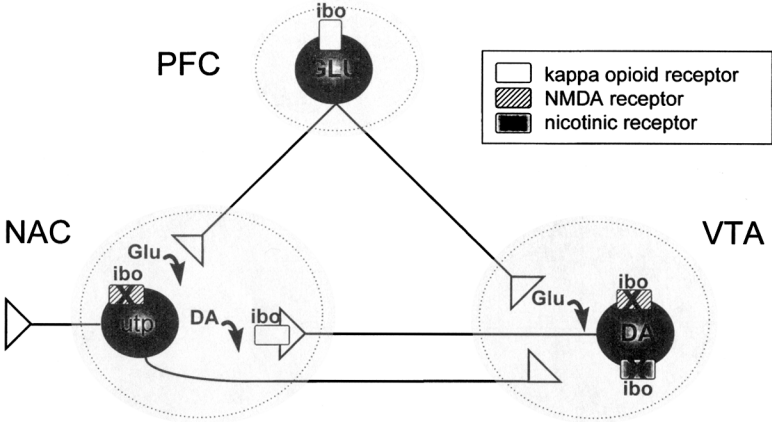


FIGURE 5. Proposed scheme in which kappa opioid agonist, NMDA antagonist and nicotinic antagonist effects of ibogaine and/or noribogaine could together dampen the responsiveness of the mesolimbic system to the dopamine-enhancing actions of addictive drugs.

MK-801 can also block nicotinic sites,⁴⁰ and one wonders whether ibogaine is simply an open-channel blocker that will interfere with several such receptor systems.

While ibogaine's structural resemblance to lysergic acid diethylamide (LSD) focused early efforts on serotonergic mechanisms, the role of serotonin in mediating ibogaine's effects is especially enigmatic. The results from binding studies have been inconsistent, with some investigators reporting affinities of ibogaine for one or another serotonin receptor^{9,10} and others not finding any affinities.^{3,9} The results of drug discrimination studies with LSD have also conflicted;^{31,32} at best, there may be partial generalization between LSD and ibogaine. Noribogaine has a tenfold higher affinity for the serotonin uptake site than ibogaine,⁶ a finding we have replicated. However, with regard to increasing extracellular serotonin levels, ibogaine is much more effective than noribo-

TABLE 2. Summary of Mechanisms of Action of Ibogaine

Kappa agonist
Opioid (morphine) and stimulant (cocaine) self-administration
NMDA antagonist
Opioid self-administration
Opioid physical dependence (withdrawal)
Nicotinic antagonist
Nicotine self-administration (smoking)
Serotonin uptake inhibitor
Alcohol intake
Hallucinations
Sigma-2 agonist
Cerebellar neurotoxicity
Lipid solubility and metabolism
Long-term effects

gaine,²⁷ despite noribogaine's greater potency. We believe that ibogaine is most probably a serotonin-releasing agent. However, compared to its effects on brain dopamine systems, the effects of ibogaine on brain serotonin systems seem to be more transient, dissipating in three hours, while at least some of the dopamine effects persist for 24 hours or more. The serotonergic effects of ibogaine might therefore mediate some of the shorter-lasting effects of ibogaine, for example, effects on alcohol intake as well as possibly the hallucinogenic manifestations typically reported during the early hours after ibogaine treatment in people.

It has been generally assumed that glutamate is involved in the mechanism of ibogaine-induced neurotoxicity. Ibogaine has been thought to activate the olivary-cerebellar pathway, causing the release of glutamate at Purkinje cells in the vermis. The excessive glutamate resulting from high doses of ibogaine would then be neurotoxic. Consistent with this theory, the NMDA antagonist MK-801 was reported to attenuate ibogaine-induced loss of cerebellar Purkinje cells.⁴¹ This, of course, seems somewhat paradoxical, since ibogaine itself appears to be an NMDA antagonist. The recent reports that ibogaine binds to sigma-2 receptors^{2,5,39} and that a sigma-2 agonist action of ibogaine is responsible for its neurotoxicity³⁸ may be the key to this puzzle. The affinity of ibogaine for the sigma-2 site is much higher than its affinity for the NMDA site. Ibogaine-induced release of glutamate in the cerebellum via activation of sigma-2 receptors might produce the cerebellar damage, thus precluding any potential neuroprotective effect stemming from ibogaine's NMDA antagonist action.

The last issue that needs addressing is the mechanism of ibogaine's long-term effects. Our initial findings that ibogaine had such effects^{12,18} led us to speculate that ibogaine might have an active and persistent metabolite. It was subsequently demonstrated that ibogaine did indeed have an active metabolite,^{6,7,11} namely, 12-hydroxyibogamine or noribogaine. While a report of one human patient⁶ indicated that noribogaine persisted in plasma at high levels for at least 24 hours after oral ibogaine administration, it was not clear if this response was typical or atypical (see Mash, this volume). Recent reports^{43,44} indicate that noribogaine levels in plasma as well as in brain progressively decline from five to 24 hours after ibogaine administration (i.p.) in rats, although levels in brain may still be high enough (2–5 μ M) at 24 hours to mediate pharmacological effects. One important contributor to this mechanism is the fact that ibogaine is sequestered in fat⁴⁴ and possibly in other body depots. For example, whole blood levels⁴³ appear to be much higher than plasma levels,⁴² suggesting that platelets may also sequester ibogaine. Slow release of ibogaine from such depots and metabolism to noribogaine may constitute the crucial events in producing long-term effects. The well-known variability in ibogaine's effects, both in animals and in humans, may depend both on the extent of fat deposition and on the extent of ibogaine metabolism to noribogaine. It is possible that in addition to ibogaine being converted to noribogaine in the liver that it might also occur in the brain. If this happened, inasmuch as noribogaine is much more polar than ibogaine, noribogaine might be trapped in the brain for a relatively prolonged period of time. Thus there are several factors that may contribute to ibogaine's long duration of action.

In summary, to reiterate what was said in the introduction, ibogaine has a complex pharmacology—but it is a pharmacology well worth studying. In a very important sense, its pharmacology represents a whole new approach to the pharmacotherapy of drug addiction. At the very least ibogaine should be considered the prototype of a new class of potentially useful antiaddictive agents. And there are already indications that the development of less toxic and more efficacious congeners (e.g., 18-methoxycoronaridine¹⁴) is possible.

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